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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Kit S. Lam and Alan L. Lehman		
Serial No.:	10/057,178	Art Unit:	1639
		Examiner:	Jon D. Epperson
Filed:	January 24, 2002		
For:	Method for Determining Differences in Molecular Interactions and for Screening A Combinatorial Library		

DECLARATION OF ALAN L. LEHMAN UNDER 37 C.F.R. SECTION 1.132 IN RESPONSE TO OFFICE ACTION MAILED JUNE 15, 2006

1. I am a project scientist at the University of California, Davis, Medical Center. I work in the Cancer Research Center where my duties include screening combinatorial bead libraries with a variety of proteins including individual cancer proteins as well as cancer cell extracts. For the past 2 years, my research has focused on the production of ligands that bind to and can be used to recognize HHS and USDA select agents and toxins. I received my Ph.D in genetics in 2000. I am one of the inventors on this pending application. Attached hereto as Exhibit A is my curriculum vitae. This declaration is submitted in response to the Office Action mailed June 15, 2006 ("the Office Action").

2. I have reviewed the following documents: this pending patent application, the Office Action, and the two items cited by the Examiner in the Office Action (the article entitled "DiffScreen: the merging of image subtraction and molecular genetics for the rapid analysis of differentially screened cDNA libraries" by Tizard and PCT international publication no. WO 01/40265 A2 of Hammond). I am familiar with the

techniques and methods described in these items and also with other literature in the field. As set forth below, I believe the amended claims are not rendered obvious by Hammond and Tizard.

3. Tizard's disclosure of B-A on a pixel-by-pixel basis and further adjusting the formula for overexposure does not disclose the use of (B-A)/A for the following reasons.

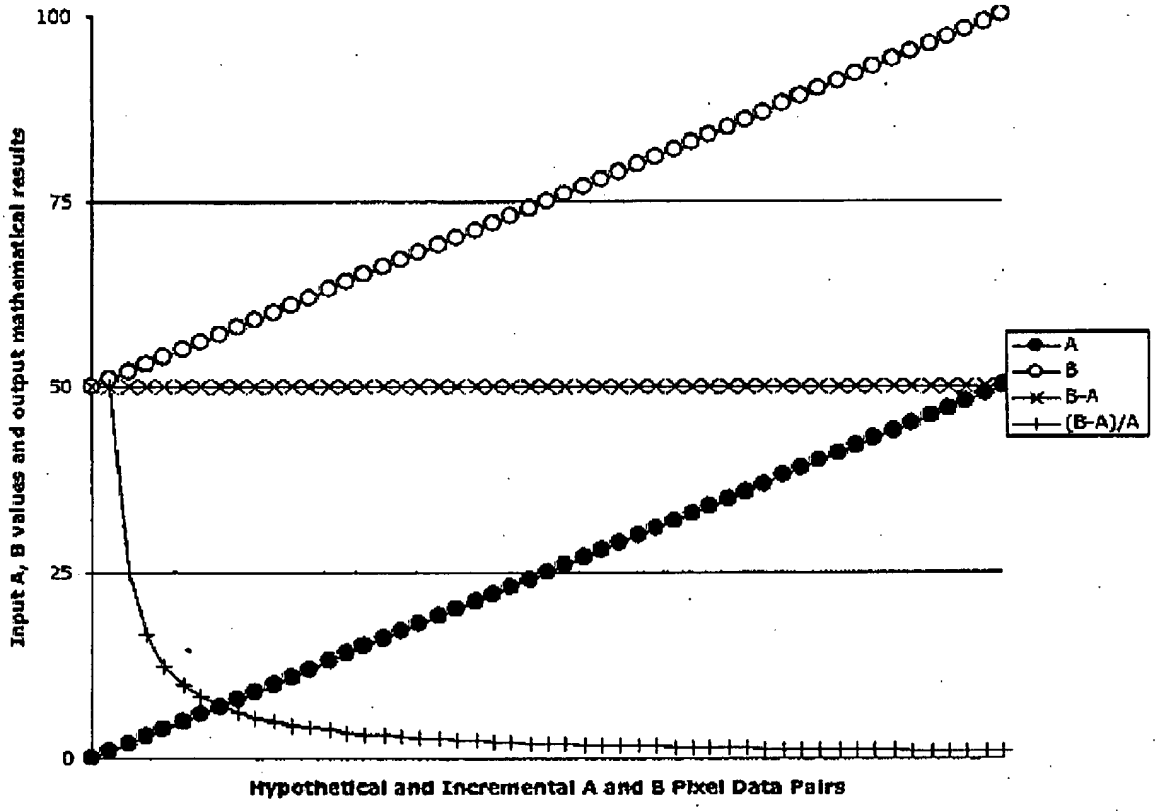
Overexposure compensation only requires a single image. This is different from the method of the invention because our method requires two images to produce the desired result. Our method does use exposure compensation on the individual images, on an as needed basis, but it occurs before the application of the (B-A)/A formula.

Exposure compensation is a linear transformation – the value of each individual pixel is reduced by a fixed amount to obtain the desired exposure. (B-A)/A is a non-linear transformation; the magnitude of change is highly dependant on the starting values.

4. The application of the formula (B-A)/A to create a third image produces dramatically different mathematical results from the formula B-A. These results are visualized in the form of an image that is denoted as image C.

As can be seen in the graph below, the mathematical result produced from the equations B-A and (B-A)/A are very different. The graph shows four data series. The solid circles represent a range of potential pixel values that might be present in a hypothetical image A, while the hollow circles represent a higher range of potential pixel values that might be found in image B. At each pair of A and B points on the graph of our hypothetical data, the pixel values differ by 50. The third data series is represented by --X--X-- and it graphs the mathematical results obtained by subtracting B-A for each of the A and B pixel value pairs. It is apparent that the calculated value never changes; the answer for each of the A and B data pairs is always 50. The fourth series is represented by -+-+- and it graphs the mathematical result obtained by applying the (B-A)/A formula to each of the A and B pixel value pairs. In contrast to the mathematical results obtained from B-A, the mathematical results obtained from (B-A)/A vary dramatically between the different A and B data pairs in the graph below. As the value of A increases, the

mathematical result obtained from (B-A)/A decreases in a non-linear fashion. In other words, (B-A)/A applies a numerical penalty for not having an A pixel value of nearly zero.



As set forth in the table below, using the B-A formula, it is impossible to distinguish the mathematical results for the following pairs of A and B pixel values: A=1 and B=51 versus A=25 and B=75. The mathematical result for both pairs is 50.

A pixel values	B pixel values	Formula	Result	Comment
1	51	B-A	50	A is low, B is high
25	75	B-A	50	A is high, B is higher
1	51	(B-A)/A	50	A is low, B is high
25	75	(B-A)/A	2	A is high, B is higher. Mathematical result of (B-A)/A shows clear distinction.

In contrast to the results obtained from applying B-A, the (B-A)/A formula produces dramatically different mathematical results. For A=1 and B=51, the result is 50; while for A=25 and B=75, the result is 2. Thus, there is a significant difference in the mathematical results that depends on whether the A value is high or nearly zero. It is this dependence on the A value being very close to zero that allows us to screen out and eliminate from consideration all the value pairs that do not contain A values that are nearly zero. If the A and B values represent the intensities of signals obtained from screening combinatorial bead libraries, the equivalent statement would be that the (B-A)/A formula allows us to screen out and eliminate from consideration any beads with detectable signal in both A and B images. We are left with results that highlight beads that have zero or very low signal (pixel value) in the A image and higher signal (pixel value) in the B image. Applying the simple formula B-A would not accomplish this.

In summary, the formula B-A does not distinguish between data pairs consisting of A pixel values that start low and B pixel values that end high, and A values that start high and B values that end higher. In contrast, the formula (B-A)/A clearly distinguishes between those same data pairs by diminishing the mathematical result of any A and B pixel value pairs where the A value is not low.

The distinction between (B-A)/A and B-A is critical as this method is used to determine the differences between the molecular interactions of two different mixtures of

molecules, such as a first mixture of protein extract from normal cells and a target mixture of protein extract from cancer cells. Image A will show beads that have bound molecules of the first mixture (which could include molecules unique to the first mixture and molecules common to both the first mixture and the target mixture) and beads that are referred to as false positives (beads that have bound reagents used in the method). Image B will show all of the beads of image A plus beads that have bound molecules unique to the target mixture. Image C is created by applying the formula (B-A)/A on a pixel-by-pixel basis; it shows those beads that have bound molecules unique to the target mixture (referred to as true positives). The /A step emphasizes the true positive beads by giving much greater weight to beads not marked in image A but marked in image B, and lesser weight to beads marked in both image A and image B. Stated another way, greater weight is given to beads that have bound molecules unique to the target mixture than beads that have bound molecules common to both mixtures. Where, for example, the first mixture is a normal cell extract and the target mixture is a cancer cell extract, this distinction is of crucial significance because it identifies the beads (and therefore the ligands) that bind molecules that are unique to cancer cells.

5. I hereby state that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code.

Dated: November 15, 2006

/Alan Lehman/

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Education:

Ph.D. in Genetics, University of California - Davis (2000)
Bachelor of Science - Genetics, University of Kansas (1992)
Bachelor of Arts (Honors), University of Kansas (1991)

Research Experience:

Post Doctoral Research, University of California – Davis Medical Center. Applications of Combinatorial Chemistry Techniques to Cancer Research, laboratory of Dr. Kit S. Lam (2000-present).

Graduate Research, University of California - Davis. Dissertation: "The CTD Phosphatase Sensitivity of RNA Polymerase II," laboratory of Dr. Michael Dahmus (1993-2000).

Undergraduate Research, University of California - Davis. Cloning and sequencing of genes related to Fanconi anemia, laboratory of Dr. James Boyd (1992).

Undergraduate Research, University of Kansas. Cloning and sequencing of genes related to systemic lupus erythematosus, laboratory of Dr. Dean Stetler (1991).

Publications:

Lehman, AL and Lam, KS, (submitted to JCC) Novel image subtraction approach to screening one-bead one-compound combinatorial libraries with complex protein mixtures.

Sung Hee Hwang, Alan Lehman, Xin Cong, Olmstead, Kit S. Lam, Carlito B. Lebrilla, Mark J. Kurth, Organic Letters, 2004 Oct 14;6(21):3829-32., OBOC Small Molecule Combinatorial Libraries Encoded by Halogenated Mass-Tags

Lam KS, Lehman AL, Song A, Doan N, Enstrom AM, Maxwell J, Liu R., Methods Enzymol., 2003, 369, 298-322, Synthesis and screening of "one-bead one-compound" combinatorial peptide libraries.

Lam KS, Liu R, Miyamoto S, Lehman AL, Tuscano JM., Acc Chem Res. 2003 Jun, 36(6), 370-7, "Applications of one-bead one-compound combinatorial libraries and chemical microarrays in signal transduction research."

Lehman, A.L. & Dahmus, M.E., J. Biol. Chem. 2000, 275, 14923-32, "The Sensitivity of RNA Polymerase II in Elongation Complexes to C-Terminal Domain Phosphatase".

EXHIBIT A

Lehman, A.L. & Lehman, T.A., Amer. Jour. Phys. 1988, 56, 1046, "An Illustration of Buoyancy in the Horizontal Plane".

Patents:

Kit S. Lam and Alan L. Lehman, Novel Screening Method for Combinatorial Compound-Bead Libraries, (Patent Pending)

Active Collaborations:

Rod Balhorn, Division Leader for Molecular Biophysiology, Lawrence Livermore National Laboratory
David M. Wilson III, Laboratory of Molecular Gerontology, GRC, National Institute on Aging, IRP, NIH
Mark Kurth, Professor, Department of Chemistry, University of California, Davis.
Kwan-Liu Ma, Professor, Institute for Data Analysis and Visualization, University of California, Davis.
Bo Lonnerdal, Department of Nutrition, Internal Medicine, University of California, Davis.
Tom North, Professor, Center for Comparative Medicine, University of California, Davis.

Research Presentations:

Poster presentation at the UCDMC Caner Center Symposium (2005).
Poster presentation at the Society for Biomolecular Screening Conference & Exhibition (2003)
Poster presentation at the 23rd Symposium on Transcription - Cold Spring Harbor Laboratories (1998).
Invited Speaker at the University of California - Davis, Molecular and Cellular Biology Fall Colloquium (1996-1998).

Professional Affiliations

The Society of Biomolecular Screening (2002-present)

Additional Professional Training:

Business Intensive course-UCD Graduate School of Management, 2005
UCD-GSM Big Bang Business Plan Competition, Awarded People's Choice business plan (2003).
PERL for Biologists-University Extension, UC-Davis, 2002
Bioinformatics II-The UC Davis Biotechnology Program, 2001
Protein and Proteome Analysis- The UC Davis Biotechnology Program, 2000
Database Design, Development & Management-University Extension, UC-Davis (2000).

Teaching Experience:

Teaching Assistant, University of California - Davis Introductory Biochemistry (2000)
Teaching Assistant, University of California - Davis Introductory Biology (1999)
Teaching Assistant, University of California - Davis Senior Biochemistry laboratory (1994, 1997)
Teaching Assistant, University of Kansas Chemistry laboratory (1992)

Community service:

Zone Captain, Neighborhood Response Team, 2002-Present
Sacramento County District Attorney Citizens Academy (2004)
Oak Park Neighborhood Association, 2001-Present.

References:

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